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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	

ART UNIT	PAPER NUMBER
1616	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

USPTO.e-Office.rdg@boehringer-ingelheim.com

Office Action Summary	Application No.	Applicant(s)	
	10/614,362	MEADE ET AL.	
	Examiner	Art Unit	
	JAMES H. ALSTRUM ACEVEDO	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3, 5, 7-31, 34-35, and 37* is/are pending in the application.

4a) Of the above claim(s) *9,11-19 and 34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,7,8,10,20-31,35 and 37* is/are rejected.

7)☒ Claim(s) *1* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-3, 5, 7-31, 34-35, and 37 are pending. Applicants amended claims 1, 5, and 37. Applicants newly cancelled claims 4 and 6. Applicants previously cancelled claims 32-33 and 36. Claims 9, 11-19, and 34 are withdrawn from consideration as being drawn to non-elected subject matter. **Claims 1-3, 5, 7-8, 10, 20-31, 35, and 37 are under consideration in the instant office action.** Receipt and consideration of Applicants' arguments/remarks submitted March 19, 2009 are acknowledged. All rejections not explicitly maintained in the instant office action have been withdrawn per Applicants' claim amendments and/or persuasive arguments.

Election/Restrictions

It is noted that Applicants' claim amendments have stricken the elected species of NK_1 receptor antagonist from the pending claims. The species election has been expanded to include (S)-N-[2-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-4-(cyclopropylmethyl)-N-methyl-a-phenyl-1-piperazineacetamide as the elected NK_1 receptor antagonist.

Priority

Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Specification

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Objections

Claim 1 is objected to because of the following informalities: a comma should be inserted between the first and second compounds listed in item (b) of claim 1 (i.e. between the "piperazineacetamide" and "(+)-..." Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, 7-10, 20-31, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the *written description requirement*. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Determination of Claim Scope

Claims 1 and 37 of the instant application claim (A) a pharmaceutical composition

comprising (i) one or more anticholinergics of formula 1, including any hydrate thereof and (ii) one or more NK1 receptor antagonist selected from a group of about 13 specific compounds and (B) a method of treatment of chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) contained in separate pharmaceutical formulations, respectively.

Review of Applicants' Disclosure

The instant specification does not disclose, to which solvates or hydrates of any anticholinergic of formula 1 Applicants are referring. Applicants' specification does not disclose how to make any particular hydrate of any anticholinergic of formula 1, nor do Applicants depict chemical structures of any anticholinergic of formula 1 as any particular hydrate in their disclosure.

Possession Based on Ordinary Skilled Artisan's Determination/ State of the Prior Art

It is generally accepted in the art that the formation of a particular hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 18), therefore, the generic reference to a hydrate of the anticholinergics of Applicants' formula 1 in the instant specification does not provide adequate written support for claims drawn to hydrate of these compounds. An ordinary skilled artisan would conclude that Applicants were not in possession of any particular hydrate of any anticholinergic of formula 1. Furthermore, because Applicants' generic reference to hydrates of any anticholinergic of formula 1 or any NK1 receptor antagonist does not permit the ordinary skilled artisan to clearly envisage which specific hydrate, if any, of any anticholinergic of

formula 1 was in Applicants' possession, the only reasonable conclusion said artisan would make was that Applicants were not in possession of the genus of hydrates of any anticholinergic of formula 1 and had not reduced to practice the preparation, isolation, and characterization of said genus of hydrates.

The remaining claims are rejected as depending from a rejected claim.

Response to Arguments

Applicant's arguments filed 3/13/09 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that (1) Applicants' reasonably conveys to the ordinary skilled artisan that Applicants were in possession of the genus of hydrates of anticholinergics of formula 1, because Applicants' specification has a generic reference to said hydrates, the original claims made a generic reference to hydrates, and based upon the conventional knowledge of hydrates in the art; (2) the essential and critical feature of the compounds of formula 1 is the base structure and not whether it is a hydrate or not; (3) the Applicants' enablement discussion that merely routine experimentation would be needed to ascertain which hydrates of the anticholinergics of Applicants' formula 1 could be obtained and/or exist is evidence of adequate written description.

Applicants' arguments are respectfully found unpersuasive. Regarding (1), a laundry list of every possible polymorphic species (e.g. solvates and hydrates) does not constitute an adequate written description, because it would not reasonably lead those skilled in the art to a specific hydrate (i.e. a specific compound of Applicants' formula 1 in the form of a specific hydrate (e.g. a monohydrate or pentahydrate)). The mere inclusion of the word "hydrates" in the specification or an original claim is not evidence of possession, given that it is conventionally

accepted in the art that one cannot know *a priori* whether a specific compound or genus of specific compounds form hydrates. Thus, to meet the written description requirement for hydrates Applicants' specification requires more than the generic inclusion of the words, "hydrates thereof." An invitation to the ordinary skilled artisan to experiment to ascertain whether hydrates of compounds of formula 1 can be obtained does not meet the requirements of adequate written description.

Regarding (2), if the recitation of "hydrates" of compounds of formula 1 were not an essential and critical feature of Applicants' invention, then one would reasonably expect that Applicants would not vigorously argue to maintain the word "hydrates" in reference to compounds of formula 1 in their claims. Given that Applicants have vigorously argued to maintain the recitation of "hydrates" of compounds of formula 1 in their claims as being proper, one can only conclude that Applicants deem "hydrates" to be an essential and critical element of their claimed invention. Thus, it is concluded that the recitation of hydrates of compounds of formula 1 is an essential and critical feature of the claimed compositions that requires adequate description in Applicants' specification.

Regarding (3), Applicants' traversal arguments concerning the enablement rejection never provide evidence that Applicants possessed even a single specific hydrate of any compound of formula 1 or were even aware which compounds of formula 1 could form hydrates or how many different hydrates (e.g. monohydrates, dihydrates, channel hydrates, pentahydrates, etc.) of a particular compound of formula 1 could be isolated and characterized. Thus, Applicants' enablement arguments, which are always written with a speculative tone about what an ordinary skilled artisan may or may not be able to ascertain through alleged routine

experimentation supports the instant written description rejection and the conclusion that Applicants were not in possession of the genus of hydrates of compounds of formula 1.

Claims 1-3, 5, 7-10, 20-31, 35, and 37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compositions comprising component (a) in the form of enantiomers, racemates, and mixtures of enantiomers, does not reasonably provide enablement for compositions comprising hydrates of any species of compounds of component (a). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co*., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims

Applicants' claims are broad with regards to the subgenera of hydrates, enantiomers, racemates, and mixtures of enantiomers of one or more anticholinergic of formula 1.

Nature of the invention/State of the Prior Art

Claims 1 and 37 of the instant application claim (A) a pharmaceutical composition comprising (i) one or more anticholinergics of formula 1, including a hydrate thereof and (ii) one or more NK1 receptor antagonist and (B) a method of treatment of chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) contained in separate pharmaceutical formulations, respectively, are representative of the nature of Applicants' invention. It is generally accepted in the art that the formation of a particular hydrate for a given compound or series of compounds is unpredictable (see Vippagunta et al. "Crystalline Solids," *Advanced Drug Delivery Reviews*, **2001**, *48*, pp 11 and 18).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970). The art is especially unpredictable with regards to the existence and formation of particular polymorphs and pseudopolymorphs (e.g. hydrates and solvates) of chemical compounds, as set forth above by the teachings of Vippagunta et al.

Guidance/Working Examples

Applicants provide no guidance or working examples about the preparation of any solvate or hydrate of Claims 1 and 37 of the instant application claim (A) a pharmaceutical composition comprising (i) one or more anticholinergics of formula 1, including a solvate or hydrate thereof and (ii) one or more NK1 receptor antagonist, including a solvate or hydrate thereof and (B) a method of treatment of chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) contained in separate pharmaceutical formulations, respectively.

In conclusion, the specification, while being enabling for compositions comprising components (i) and (ii) in the form of enantiomers, racemates, and mixtures of enantiomers, and methods of treating COPD by administering said components, does not reasonably provide enablement for compositions comprising solvates or hydrates of Claims 1 and 37 of the instant application claim (A) a pharmaceutical composition comprising (i) one or more anticholinergics of formula 1, including a solvate or hydrate thereof and (ii) one or more NK1 receptor antagonist, including a solvate or hydrate thereof and (B) a method of treatment of chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) contained in separate pharmaceutical formulations, respectively.

Response to Arguments

Applicant's arguments filed 3/13/09 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by arguing that (1) the analysis in the instant rejection posed the wrong question and should have asked whether routine

experimentation could be used to obtain hydrates of compounds of Applicants' formula 1; (2) the definition of hydrates and the chemical formula of any theoretically possible hydrate of Applicants' compounds of formula 1 is well known to the ordinary skilled artisan; (3) it is conventional to provide hydrates of compounds of Applicants' formula 1; (4) only routine experimentation is needed to ascertain if any of Applicants' compounds of formula 1 do indeed form a hydrate and to know which specific kinds of hydrates are formed; and (5) water is a known solvent in pharmaceutical applications.

In response to Applicants' arguments, Applicants are directed to Braga et al. (*Chem. Commun.*, "Making Crystals from Crystals: a green route to crystal engineering and polymorphism," **2005**, pp 3635-3645), which states on page 3640, "One can say that if the formation of polymorphs is a nuisance for crystal engineers, solvate formation can be a nightmare, because it is extremely difficult to predict whether a new species may crystallize[s] from solution with one or more molecules of solvent." Hydrates are a subgenus of solvates. Therefore, Braga's statement concerning solvates is equally relevant to hydrates, and the ordinary skilled artisan would be unduly burdened to obtain a particular hydrate, let alone the genus of hydrates claimed by Applicants. It is reiterated that there is no way of knowing whether all, none, or only certain compounds of formula 1 can form hydrates a priori and that to ascertain, which specific hydrates of Applicants' compounds of formula 1 could be obtained would be unduly burdensome. Something that is a considered "a nightmare" by the ordinary skilled artisan does not fall within the purview of routine experimentation.

Applicants' arguments seem to simplify the recitation of a hydrate to a mere word or inclusion of "H_2O" in a chemical formula written on a piece of paper. This is an

oversimplification and ignores the fact that hydrates refer to specific polymorphs characterized by specific crystalline unit cells and exhibiting specific and often significantly different physical properties. Furthermore, it is generally recognized that different polymorphs of the same compound exhibit different physical properties, although the different polymorphs can be written with the same "chemical formula" on a piece of paper. Thus, reference to hydrates is more meaningful than the inclusion of a molecule of water or many molecules of water in the chemical formula of a compound of Applicants' formula 1 written on a piece of paper. Applicants' arguments are found unpersuasive and the instant rejection is maintained.

The remaining claims are rejected as depending from a rejected claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-3, 5, 7-10, 20-26, 28-31, 35, and 37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner et al. (US 2002/0115680) in view of Dollinger et al. (WO 02/32865) (IDS reference) and Podolsky (US 2003/0185838) (already of record).

NOTE: U.S. Patent No. 6,747,044 is an English language equivalent of WO 02/32865 (Dollinger-US).

Applicants Claim

Applicants claim (A) a pharmaceutical composition comprising (i) one or more anticholinergics of formula 1, including a solvate or hydrate thereof and (ii) one or more NK1 receptor antagonist, including a solvate or hydrate thereof and (B) a method of treatment of chronic obstructive pulmonary diseases (COPD) comprising administering (i) and (ii) separately or together in a pharmaceutical formulation to a patient in need thereof.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

Meissner teaches **the administration of anticholinergic compounds of formula I, to treat chronic obstructive pulmonary disease (COPD)** (title; abstract; [0004], [0172]; [0184]; [0188]; and claim 7). **Applicants' specific anticholinergic of formula 1 is disclosed explicitly by Meissner as a compound of particular importance ([0049] and [0051])**. Meissner discloses the synthesis of Applicants' anticholinergic compound of formula 1 in Example 1([0103]-[[0108]). Meissner discloses that pharmaceutical formulations of the invented anticholinergic compounds may be in the form of solutions [0184] and the solutions are prepared in the usual way with the addition of isotonic agents (e.g. NaCl), preservatives (e.g. p-hydroxybenzoates), stabilizers (e.g. alkali salts of EDTA), diluent (e.g. water), and organic solvents [0186]. An exemplified **aqueous propellant-free formulation is disclosed in Example C and comprises active substance (i.e. Meissner's invented anticholinergic compounds), sodium chloride (i.e. an isotonic agent), and water (i.e. a diluent)** (between paragraphs [0193]-[0194]). The active substance is prepared by dissolution in water, optionally adjusting the pH to a value of 5.5 to 6.5, and addition of sodium chloride [0194]. Example E discloses an **aqueous formulation with a pH of 3.4 comprising active substance (333.3 mg), formoterol fumarate (333.3 mg), benzalkonium chloride (10.0 mg), EDTA (50.0 mg), 1N HCl (added in an amount sufficient to result in a pH of 3.4)** [0195]-[0196]. In general, suitable amounts of Meissner's invented anticholinergic compounds are in the range of **0.05-90% w/w [0184] or in an amount from 1-1,000 mg** [0189]. The invented anticholinergic compounds **are characterized by high efficacy even in the microgram amount** [0189]. Syrups or elixirs (i.e. liquid formulations) comprising the active substances may additionally contain sweeteners (e.g. saccharine, glycerol, or sugar) and **flavorings** (e.g. vanilla orange

extract) [0185]. The compositions may also contain **suspension adjuvants, wetting agents, and preservatives** [0185].

Dollinger discloses the preparation of **(S)-N-[2-[3,5-bis-(trifluoromethyl)phenyl]ethyl]-4-(cyclopropylmethyl)-N-methyl-a-phenyl-1-piperazineacetamide, a NK_1 receptor antagonist on page 17, lines 28-31.** Dollinger also teaches how to obtain the racemic form of this compound, its HCl salt, and other derivatives from page 16, line 13 through page 17, line 26 (i.e. Example 3 [Beispiel 3]). See also the first compound in claim 9 of Dollinger. See also Example 3 in Dollinger-US: col. 11, line 56 through col. 12, line 67, especially col. 12, lines 62-67. Dollinger's invented compounds **are identified as NK1 receptor antagonists** (title; abstract; pg. 2, lines 1-4: In Dollinger-US see title; abstract, col. 1, lines 45-50) and **are indicated for the treatment of a variety of diseases, including COPD** (pg. 4, lines 21-32 and pg. 5, lines 20-24: In Dollinger-US see col. 3, lines 23-30 and 57-60). **Dollinger states that the invented compounds are particularly well suited for the treatment and/or prevention of COPD** or depression due to their long-lasting activity) (pg. 5, lines 20-24: Dollinger-US col. 3, lines 57-60). Dollinger indicates a preference for racemates and the (S)-enantiomer (pg. 4, lines 21-24: Dollinger-US, col. 3, lines 19-22).

Podolsky teaches methods and compositions for treatments of lesions of the respiratory epithelium comprising trefoil peptide alone or in combination with additional therapeutic agents (e.g. **neurokinin receptor antagonists**) (title; abstract; [0010]-[0013], and claim 28), and expressly teaches the administration of neurokinin receptor antagonists in combination with trefoil peptides **in the treatment of COPD** (see [0010]; [0032]; and claims 1, 5, and 16).

Neurokinin receptor antagonists and cholinergic receptor antagonists (i.e. anticholinergics) are explicitly identified as being bronchodilating agents [0065].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meissner lacks the teaching of compositions comprising NK1 receptor antagonists and the administration of said compounds to treat COPD. This deficiency is cured by the teachings of Dollinger and Podolsky.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify Meissner's compositions to comprise one or more neurokinin 1 (NK1) receptor antagonist (Dollinger), because neurokinin receptor antagonists are known and are indicated for the treatment of COPD (Podolsky and Dollinger). An ordinary skilled artisan would have been motivated to combine the prior art teachings because Meissner's anticholinergic compounds are indicated for the treatment of COPD and neurokinin antagonists, such as, Dollinger's neurokinin 1 antagonists, are indicated for the treatment of COPD as well. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose, in order to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). An ordinary skilled artisan would have had a reasonable expectation of successfully combining the prior art compositions to obtain

formulations suitable for the treatment of COPD, because Meissner's invented anticholinergic compounds are indicated for the treatment of COPD and neurokinin antagonists, such as Dollinger's invented neurokinin antagonists are indicated for the treatment of COPD.

Regarding the amounts of the anticholinergic compounds of Applicants' formula 1 and the NK1 receptor antagonists, the amount of a specific ingredient in a composition is clearly a result effective parameter that a person of ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. It would have been customary for an artisan of ordinary skill to determine the optimal amount of each ingredient needed to achieve the desired results. Thus, absent some demonstration of unexpected results from the claimed parameters, the optimization of ingredient amounts would have been obvious at the time of applicant's invention. It is noted that Applicants' specification contains no data or other objective evidence regarding the properties of the claimed compositions and associated methods of treating COPD. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicant's arguments filed 3/13/2009 have been fully considered but they are not persuasive. Applicants have traversed the instant rejection by attacking the references individually and arguing that (1) the combined references, especially Dollinger, do not teach any of the NK1 receptor antagonists recited in Applicants' claims; (2) Podolsky is allegedly deficient

because it addresses the treatment of a possible symptom of COPD (i.e. lesions of the epithelium), which Applicants equate to the absence of a teaching of the treatment of COPD; (3) Podolsky is allegedly further deficient because it does not expressly teach administration of anticholinergics and NK1 antagonists in combination to treat COPD; (4) the treatment of a symptom of COPD would not be recognized by the courts as being equivalent to the treatment of the underlying disease as allegedly supported by Rapoport v. Dement, USPQ2d 1215 (Fed. Cir. 2001); (5) allegedly the combined teachings of the prior art would not have motivated the ordinary skilled artisan to combine anticholinergics and NK1 antagonists into the same formulation intended for the treatment of COPD.

The Examiner respectfully disagrees with Applicants' traversal arguments. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Regarding (1), Dollinger explicitly teaches the first NK1 receptor antagonist compound in Applicants' amended claim 1 and Dollinger's compounds are all identified as being NK1 receptor antagonists suitable for the treatment of COPD (e.g. title; abstract; pg. 2, lines 1-4; g. 4, lines 21-32 and pg. 5, lines 20-24). Thus, the combined prior art does identify at least one of Applicants' specifically recited NK1 receptor antagonist compounds and indicates that said compounds are suitable for the treatment of COPD. Applicants' arguments are unpersuasive.

Regarding (2)-(3), Podolsky expressly discloses the combination of trefoil peptides with NK antagonists (see Podolsky's claim 27) and expressly suggests this combination in paragraph

[0062]. Furthermore, often, the underlying cause of COPD is smoking. Podolsky explicitly exemplifies the treatment of lesions caused by smoke inhalation in Example 8 ([0091]) and indicates that the primary focus of treatment is to maintain an open airway (i.e. this treats the underlying disease of Chronic Obstructive Pulmonary Disorder, which manifests as an obstruction of the airways due to bronchoconstriction). Podolsky explicitly identifies NK antagonists as bronchodilators. Clearly, the ordinary skilled artisan would find it obvious to administer a bronchodilator to treat the bronchoconstriction (i.e. obstruction), which is a fundamental characteristic of Chronic Obstructive Pulmonary Disorder (i.e. COPD).

Regarding (4) and the reliance by Applicants upon *Rapoport v. Dement*, the facts of *Rapoport* are not on point with the facts of the instant case. In *Rapoport*, the Federal Circuit considered whether a non-patent literature (NPL) reference to Rapoport discussing the treatment of anxiety by administration of buspirone rendered obvious the claimed method of the Dement' 325 application drawn to a method of treating sleep apneas by administering buspirone. The Federal Circuit concluded that the Rapoport NPL did not anticipate nor suggest the claimed method of Dement's '325 application and explicitly indicated that their conclusion was based upon the written description of the Dement '325 application, which explicitly described a method for treating sleep apnea by administration of buspirone prior to sleep. Thus, the Federal Circuit concluded that the disclosure in Dement '325 application explicitly described a claimed method of treating the underlying cause of sleep apnea and that the phrase "treatment of sleep apneas" was limited to the treatment of the underlying disease, exclusive of the treatment of associated symptoms. In the instant application, Applicants' disclosure at paragraphs [0059]-[0060] explicitly indicates that the treatment of COPD includes the treatment of complications thereof

(i.e. symptoms). Thus, a reasonable broad interpretation of treatment of COPD includes the treatment of COPD-associated symptoms. Applicants' arguments are unpersuasive.

Regarding (5), the combined prior art teachings explicitly teach that NK1 receptor antagonists are particularly suited for the treatment and/or prevention of COPD, due to their long-acting properties (Dollinger). Thus, there is a clear motivation to combine two compounds known to be suitable for the treatment of COPD, namely the anticholinergic of Applicants' formula 1 and the first NK1 receptor antagonist compound listed in Applicants' claim 1. *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). Applicants' arguments are unpersuasive and the instant rejection is maintained.

Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meissner et al. (US 2002/0115680) in view of Dollinger et al. (WO 02/32865) (IDS reference) and Podolsky (US 2003/0185838) (already of record) as applied to claims 1-3, 5, 7-10, 20-26, 28-31, 35, and 37 above, and further in view of Freund et al. (US 2001/0008632).

Applicants Claim

Applicants claim a pharmaceutical composition, as described above, further comprising an antioxidant selected from ascorbic acid, Vitamin A, Vitamin E, or tocopherols.

Determination of the Scope and Content of the Prior Art (MPEP §2141.01)

The teachings of Meissner, Dollinger, and Podolsky are set forth above.

Freund teaches aqueous propellant-free pharmaceutical solutions comprising **any**

substance suitable for the treatment of respiratory diseases by inhalation administration (title; abstract; [0001]; [0007]), such as betamimetics, **anticholinergics,** antiallergics, etc. Usually pharmaceuticals intended for inhalation are dissolved in **an aqueous or ethanolic solution**, according to the solution characteristics of the active substance [0004]. Other suitable solvents for inclusion in the formulations include **isopropyl alcohol, polyethylene glycol, glycerol**, etc. [0005]. The compositions comprise complexing agents, such as EDTA, disodium EDTA, citric acid, ascorbic acid, and nitriloacetic acid [0011]. The compositions **may also comprise additional adjuvants, such as preservatives (e.g. benzalkonium chloride)** [0010].

Ascertainment of the Difference Between Scope the Prior Art and the Claims (MPEP §2141.012)

Meissner lacks the teaching of compositions comprising an antioxidant, such as, ascorbic acid. This deficiency is cured by the teachings of Freund.

Finding of Prima Facie Obviousness Rationale and Motivation (MPEP §2142-2143)

It would have been prima facie obvious to modify Meissner's compositions to comprise ascorbic acid in lieu of or in addition to EDTA, because ascorbic acid is a well-known complexing agent (Freund) and Meissner teaches that the invented compositions may comprise complexing agents, such as EDTA. An ordinary skilled artisan would have been motivated to add ascorbic acid to Meissner's invented compositions and would have had a reasonable expectation of successfully obtaining suitable formulations, because ascorbic acid is a well-known complexing agent and would reasonably be expected to function as a complexing agent

alone or in combination with other complexing agents, such as EDTA. It is generally considered *prima facie* obvious to combine two compounds each of which is taught by the prior art to be useful for the same purpose (e.g. complexing agents), to form a composition which is to be used for the very same purpose. The idea for combining them flows logically from their having been used individually in the prior art. See *In re Kerkhoven*, 626, F.2d 848, 205 USPQ 1069 (CCPA 1980). Regarding the recitation in Applicants' claim that ascorbic acid is an antioxidant, this is merely an intended use of ascorbic acid, as well as a property of ascorbic acid. A compound and its properties are inseparable. Thus, the prior art is suggestive of compositions comprising ascorbic acid. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Response to Arguments

Applicants' arguments do not expressly address the instant rejection. Applicants' traversal arguments presented against the first 103 rejection discussed above are believed to be implicitly applied to the instant rejection. The Office's rebuttal of these traversal arguments is herein incorporated by reference and the instant rejection is maintained.

Conclusion

Claims 1-3, 5, 7-8, 10, 20-31, 35, and 37 are rejected. Claims 9, 11-19, and 34 are withdrawn from consideration. No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner is on a flexible schedule, but can normally be reached on M-F ~10am~5:30 pm, and Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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